

Durham Research Online

Deposited in DRO:

17 February 2016

Version of attached file:

Accepted Version

Peer-review status of attached file:

Peer-reviewed

Citation for published item:

Sato, K. and Sandford, G. and Shimizu, K. and Akiyama, S. and Lancashire, M.J. and Yufit, D.S. and Tarui, A. and Omote, M. and Kumadaki, I. and Harusawa, S. and Ando, A. (2016) 'Synthesis of fluorinated isoxazoles using Selectfluor™ : preparation and characterization of 4-fluoroisoxazole, 4,4,5-trifluoroisoxazoline and 4,4-difluoro-5-hydroxyisoxazoline systems from one-pot and multi-step processes.', *Tetrahedron*, 72 (13). pp. 1690-1698.

Further information on publisher's website:

<http://dx.doi.org/10.1016/j.tet.2016.02.026>

Publisher's copyright statement:

© 2016 This manuscript version is made available under the CC-BY-NC-ND 4.0 license
<http://creativecommons.org/licenses/by-nc-nd/4.0/>

Additional information:

Use policy

The full-text may be used and/or reproduced, and given to third parties in any format or medium, without prior permission or charge, for personal research or study, educational, or not-for-profit purposes provided that:

- a full bibliographic reference is made to the original source
- a [link](#) is made to the metadata record in DRO
- the full-text is not changed in any way

The full-text must not be sold in any format or medium without the formal permission of the copyright holders.

Please consult the [full DRO policy](#) for further details.

Accepted Manuscript

Synthesis of fluorinated isoxazoles using SelectfluorTM: preparation and characterization of 4-fluoroisoxazole, 4,4,5-trifluoroisoxazoline and 4,4-difluoro-5-hydroxyisoxazoline systems from one-pot and multi-step processes

Kazuyuki Sato, Graham Sandford, Keiji Shimizu, Satomi Akiyama, Marcus J. Lancashire, Dmitry S. Yufit, Atsushi Tarui, Masaaki Omote, Isumaro Kumadaki, Shinya Harusawa, Akira Ando

PII: S0040-4020(16)30089-8

DOI: [10.1016/j.tet.2016.02.026](https://doi.org/10.1016/j.tet.2016.02.026)

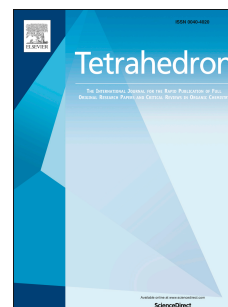
Reference: TET 27496

To appear in: *Tetrahedron*

Received Date: 14 December 2015

Revised Date: 1 February 2016

Accepted Date: 8 February 2016



Please cite this article as: Sato K, Sandford G, Shimizu K, Akiyama S, Lancashire MJ, Dmitry Yufit S, Tarui A, Omote M, Kumadaki I, Harusawa S, Ando A, Synthesis of fluorinated isoxazoles using SelectfluorTM: preparation and characterization of 4-fluoroisoxazole, 4,4,5-trifluoroisoxazoline and 4,4-difluoro-5-hydroxyisoxazoline systems from one-pot and multi-step processes, *Tetrahedron* (2016), doi: 10.1016/j.tet.2016.02.026.

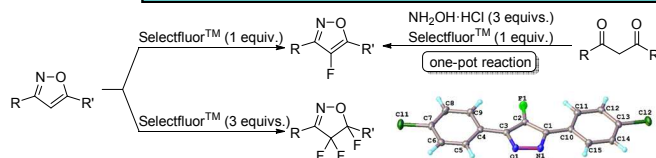
This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

Graphical Abstract

Synthesis of fluorinated isoxazoles using SelectfluorTM: preparation and characterization of 4-fluoroisoxazole, 4,4,5-trifluoroisoxazoline and 4,4-difluoro-5-hydroxyisoxazoline systems from one-pot and multi-step processes

Kazuyuki Sato^{a,b*}, Graham Sandford^{a*}, Keiji Shimizu^b, Satomi Akiyama^b, Marcus J. Lancashire^a, Dmitry S. Yufit^a, Atsushi Tarui^b, Masaaki Omote^b, Itsumaro Kumadaki^b, Shinya Harusawa^c and Akira Ando^b
^aDepartment of Chemistry, Durham University, South Road, Durham, DH1 3LE, UK. ^bFaculty of Pharmaceutical Sciences, Setsunan University, 45-1 Nagaotoge-cho, Hirakata, Osaka 573-0101, Japan. ^cOsaka University of Pharmaceutical Sciences, 4-20-1 Nasahara, Takatsuki, Osaka 569-1094, Japan

Leave this area blank for abstract info.



Synthesis of fluorinated isoxazoles using SelectfluorTM: preparation and characterization of 4-fluoroisoxazole, 4,4,5-trifluoroisoxazoline and 4,4-difluoro-5-hydroxyisoxazoline systems from one-pot and multi-step processes

Kazuyuki Sato^{a,b,*}, Graham Sandford^{a,*}, Keiji Shimizu^b, Satomi Akiyama^b, Marcus J. Lancashire^a, Dmitry S. Yufit^a, Atsushi Tarui^b, Masaaki Omote^b, Itsumaro Kumadaki^b, Shinya Harusawa^c and Akira Ando^b

^aDepartment of Chemistry, Durham University, South Road, Durham, DH1 3LE, UK

^bFaculty of Pharmaceutical Sciences, Setsunan University, 45-1 Nagaotoge-cho, Hirakata, Osaka 573-0101, Japan

^cOsaka University of Pharmaceutical Sciences, 4-20-1 Nasahara, Takatsuki, Osaka 569-1094, Japan

Abstract: 3,5-Disubstituted 4-fluoroisoxazole, 4,4,5-trifluoroisoxazoline and 4,4-difluoro-5-hydroxyisoxazoline products were obtained from reaction of the corresponding isoxazoles with SelectfluorTM depending upon the reaction conditions. Although the fluorinations proceeded using conventional heating, microwave (μ W) irradiation considerably shortened reaction times and enabled a high yielding one-pot cascade fluorination-cyclization from simple diketone substrates. In addition, a related 4-fluoroisoxazole-3-carboxamide derivative was synthesized.

Keywords: fluoroheteroaromatic; selective fluorination; 4-fluoroisoxazole; 4,4,5-trifluoroisoxazoline TRPV1 antagonist.

1. Introduction

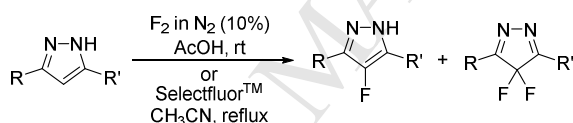
There is a continuing requirement for the development of efficient and environmentally benign routes for the synthesis of novel fluorinated aromatic and heterocyclic systems for incorporation into life science discovery programs, because many fluorinated pharmaceutical and agrochemical substances contain such structural units.¹ For the purpose of synthesizing fluorinated compounds, electrophilic fluorinating agents of the N-F class such as *N*-fluoropyridinium salts (F-Py-X),

* Corresponding author. Tel.: +81-72-866-3142; fax: +81-72-866-3142; e-mail: sato@pharm.setsunan.ac.jp

* Corresponding author. Tel.: +44-0191-334-2039; fax: +44-0191-384-4737; e-mail: graham.sandford@durham.ac.uk

SelectfluorTM and NFSI are commonly used by medicinal chemists due to the relative ease of handling these shelf-stable, solid reagents and wide commercial availability. Many fluorinated 6-membered heteroaromatic derivatives find applications in a wide variety of drugs and plant protection systems and, consequently, there are many examples of the synthesis of fluorinated 6-membered heteroaromatic rings by selective fluorination strategies in the literature as typified by the preparation of a range of fluoro-pyridine and -pyrimidine systems.^{2,3} On the other hand, selective fluorination of 5-membered heteroaromatic systems is rare and, in particular, there are only very few reports concerning the synthesis of fluorinated 5-membered heteroaromatic systems that have two ring heteroatoms, such as fluoro-pyrazoles, isoxazoles and thiazole derivatives.⁴⁻⁶

We recently reported selective fluorination of pyrazoles using fluorine gas or SelectfluorTM to give 4-fluoropyrazole or 4,4-difluoro-1*H*-pyrazole derivatives depending on the reaction conditions in moderate to good yields (Scheme 1).⁷ As part of a wider research programme aimed at synthesizing fluorinated 5-membered heteroaromatic systems, in this paper, we report our studies concerning the fluorination of isoxazoles using SelectfluorTM.



Scheme 1. Selective fluorination of pyrazoles.

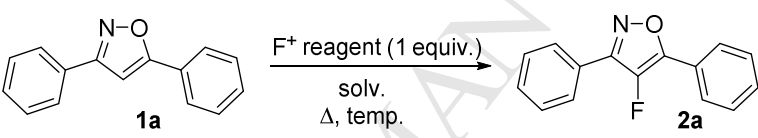
Studies concerning the synthesis of fluoroisoxazole derivatives are very rare, despite the potential utility of these systems in the life science industries. Reactions of fluorinated building blocks provide two methods for the synthesis of fluoroisoxazoles: condensation of 2-fluoro-1,3-dicarbonyl derivatives with hydroxylamine was reported by Bumgardner^{5a} and, more recently, gold catalyzed fluorocyclization of 2-alkyne *O*-methyloximes gave rise to 4-fluoroisoxazole products^{5b}. Only a very few examples of the most direct method for synthesizing fluoro-isoxazoles by electrophilic fluorination have been reported by Stephens.^{5c} Low yields of fluoroisoxazoles were prepared using SelectfluorTM and a trifluorinated system was obtained as a minor by-product in one of their syntheses. In contrast, it was reported^{5b} that attempted gold catalyzed electrophilic fluorination of 3,5-diphenylisoxazole gave no fluorinated product upon reaction with SelectfluorTM and reaction of related phenylisoxazoles with SelectfluorTM in acetonitrile were not successful, demonstrating the difficulty of carrying out such potentially simple transformations. Therefore, given conflicting

literature reports, we aimed to develop general, robust and accessible procedures for the synthesis of fluoro-isoxazoles by electrophilic fluorination reactions.

2. Results and Discussion

Following our results concerning the fluorination of pyrazoles⁷, the corresponding 3,5-diphenylisoxazole (**1a**) was fluorinated in a similar manner by using SelectfluorTM assisted by microwave (μ W) irradiation to give 3,5-diphenyl-4-fluoroisoxazole (**2a**) in moderate yield. Reaction conditions were optimized with respect to reaction time, solvent and reaction temperature as shown in Table 1.

Table 1. Fluorination of 3,5-diphenyl-4-fluoroisoxazole and reaction optimization.



Entry	Solv.	F ⁺ reagent	Heated by	Temp. (°C)	Time (min)	Yield (%) ^a
1	CH ₃ CN	Selectfluor TM	μ W	90	15	21 (19) ^b
2	CH ₃ CN	Selectfluor TM	μ W	90	60	34
3	CH ₃ CN	Selectfluor TM	μ W	150	60	38
4	CH ₃ CN	Selectfluor TM	μ W	150	120	38
5	CH ₃ CN	Selectfluor TM	μ W	200	60	37
6	CH ₃ CN	F-Py-BF ₄ ^c	μ W	150	60	nd
7	CH ₃ CN	NFSI	μ W	150	60	trace
8	CH ₃ CN	F-2,6-diClPy-OTf ^d	μ W	150	60	33
9	CH ₃ CN	F-2,6-diMePy-OTf ^e	μ W	150	60	nd
10	EtOH	Selectfluor TM	μ W	150	60	5
11	THF	Selectfluor TM	μ W	150	60	nd
12	DMF	Selectfluor TM	μ W	150	60	9
13	NMP	Selectfluor TM	μ W	150	60	nd
14	sulfolane	Selectfluor TM	μ W	150	60	42 (38) ^b
15	sulfolane	Selectfluor TM	μ W	150	15	56 (44) ^b
16	sulfolane	Selectfluor TM	oil bath	90	60	- (26) ^b
17	sulfolane	Selectfluor TM	oil bath	120	60	- (44) ^b
18	sulfolane	Selectfluor TM	oil bath	150	60	55 (42) ^b

^a ¹⁹F NMR yield calculated from benzotrifluoride (BTF) as an internal standard.

^b The numbers in parentheses show isolated yield.

^c F-Py-BF₄: *N*-fluoropyridinium tetrafluoroborate.

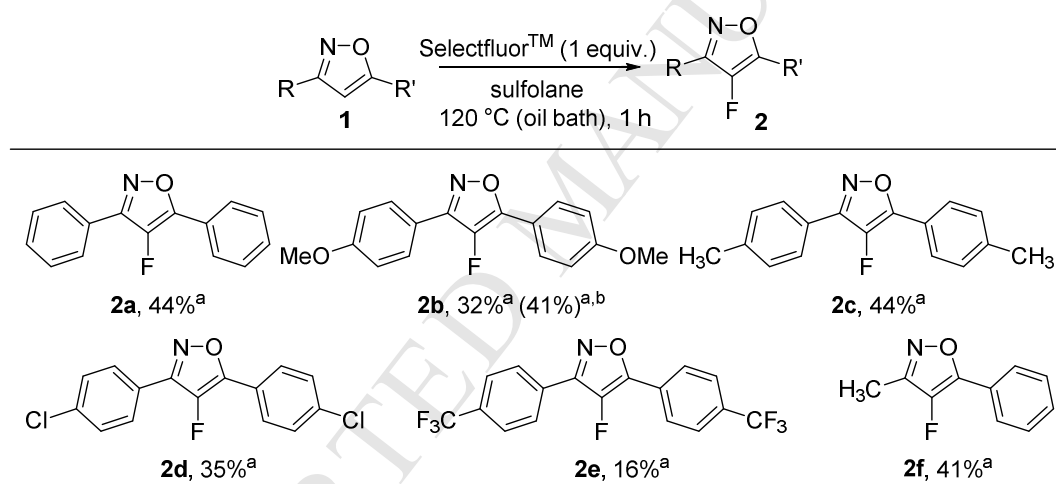
^d F-2,6-diClPy-OTf: *N*-fluoro-2,6-dichloropyridinium triflate.

^e F-2,6-diMePy-OTf: *N*-fluoro-2,6-dimethylpyridinium triflate.

Some *N*-fluoropyridinium salts (F-Py-X) and NFSI fluorinating agents were ineffective in bringing about fluorination, but the desired product (**2a**) was obtained in moderate yield by using SelectfluorTM (entries 1–9). Sulfolane was found to be the most effective solvent for this reaction (entries 10–14). In attempts to improve the yield various salts such as NaOTf, AgOTf, Sc(OTf)₃ and NaOEt were added to the reaction mixture, but these additives did not improve the yield of fluoroisoxazole product. Simple heating by conventional oil bath also gave the desired fluoroisoxazole product in similar yield as shown in entries 15–18. These results contrast with earlier reports^{5b} regarding the fluorination of reaction of (**1a**) with SelectfluorTM.

Using the optimized conditions (Table 1, entry 17 : sulfolane, 120 °C, 1 h), fluorination of several related isoxazoles were investigated and the results are summarized in Table 2.

Table 2. Selective fluorination of isoxazoles.



^a Isolated yield. ^b The reaction was carried out at 90 °C for 2 h.

3,5-Diarylisoxazoles that have electron donating group substituents gave the desired products in slightly higher yields in comparison to substrates bearing electron withdrawing groups, as would be expected for an electrophilic substitution process. A stronger donating group such as -OMe gave significant quantities of tar that decreased the yield of (**2b**), but milder reaction conditions (90 °C, 2 h) improved the yield.

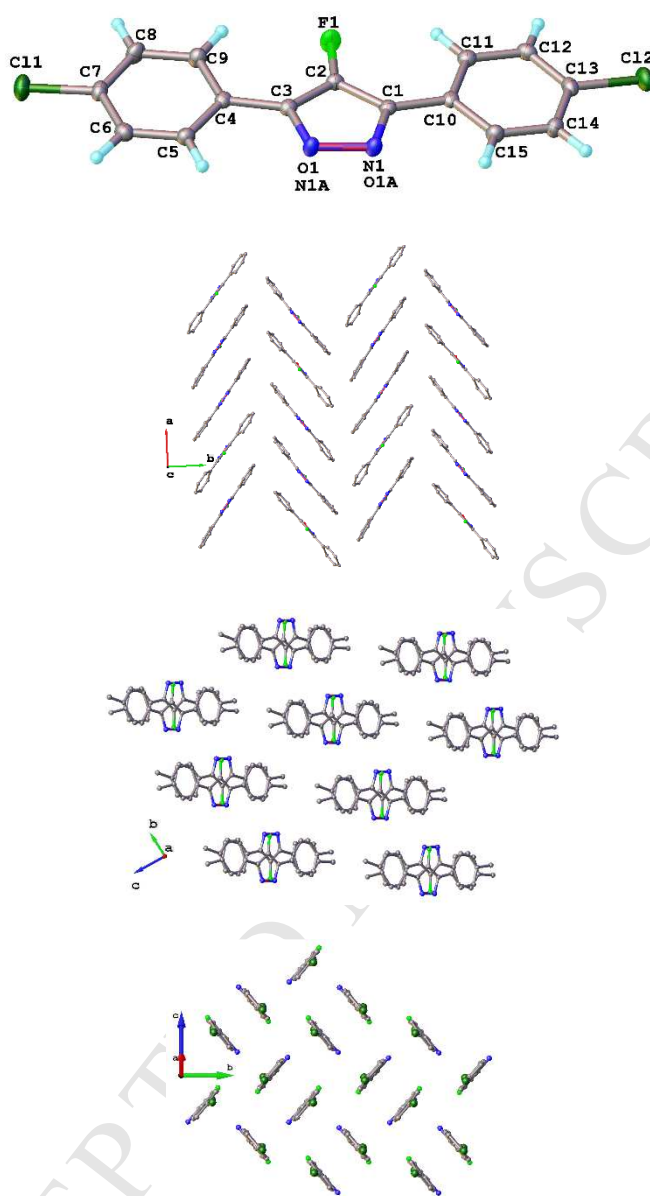


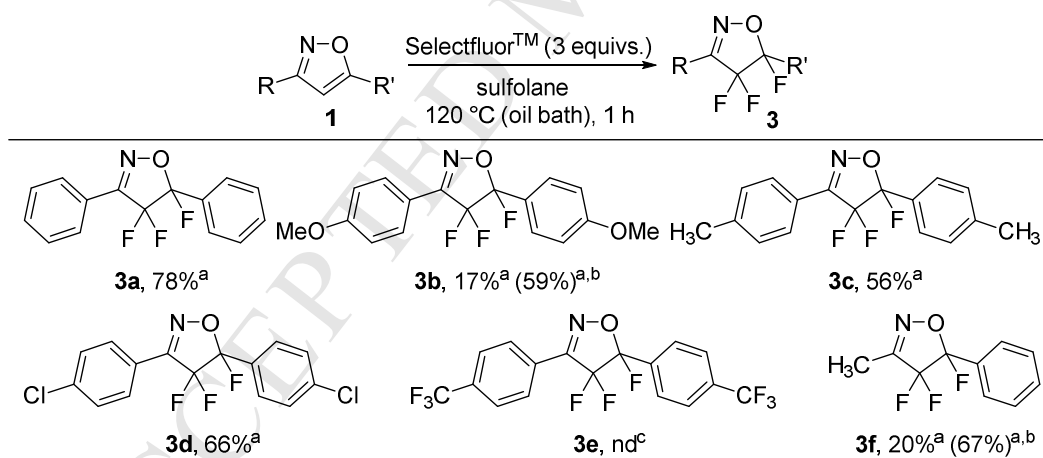
Figure 1. Molecular structure of 4-fluoro-3,5-di-(*p*-chlorophenyl)isoxazole (**2d**) and different packing motifs in crystal structures of (**2a**), (**2c**) and (**2d**).

For isoxazole substrates bearing other alkyl substituents, fluorination reactions gave the desired fluoroisoxazoles (**2c–f**) in moderate yields. All monofluorinated isoxazole products were isolated by column chromatography and characterized by NMR and mass spectrometry. In addition, the molecular structures of compounds (**2a**), (**2c**) and (**2d**) were confirmed by X-ray crystallography (Fig. 1). All these molecules are essentially planar, show similar N/O disorder in the heterocycle and $\pi\cdots\pi$ aromatic stacking interactions occur in the crystal. Nevertheless, the crystal packing in each system is quite different: molecules (**2a**) form layers of herring-bone packed molecules, in (**2c**)

disordered molecules are linked into aromatic stacks, while the layers in structure (**2d**) are constructed from herring-bone packed antiparallel dimers.

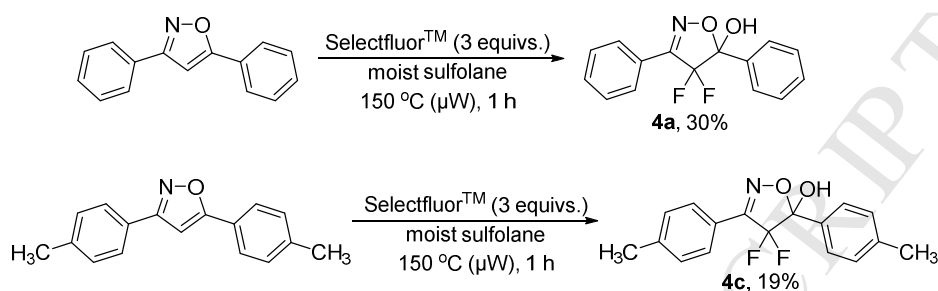
In attempts to increase the yield of the monofluorinated systems, we found that using an excess amount of SelectfluorTM gave another type of fluorinated system, 4,4,5-trifluoroisoxazolines (**3**), rather than increased amounts of 4-fluoroisoxazole products. Generation of a single 4,4,5-trifluoroisoxazoline derivative (**3**) was reported as a side product in a previous paper by Stephens and coworkers.^{5c} In our case, products (**3**) were obtained in moderate to good yields using an excess amount of SelectfluorTM and the results are summarized in Table 3. 3,5-Di-*p*-methoxyphenylisoxazole and 3-methyl-5-phenylisoxazole (**1b** and **1f**) gave a complex mixture of products and, (**3b**) and (**3f**) were obtained in low yield, respectively. The use of milder conditions in acetonitrile (reflux, 90 °C) improved the yield of the trifluorinated systems considerably. However, *p*-trifluoromethyl substituents seriously decreased the reactivity of the isoxazole substrate and, consequently, the 4-fluoroisoxazole (**2e**) was isolated in low yield rather than the trifluoroisoxazoline (**3e**).

Table 3. Selective fluorination of various isoxazoles using excess amount of SelectfluorTM.

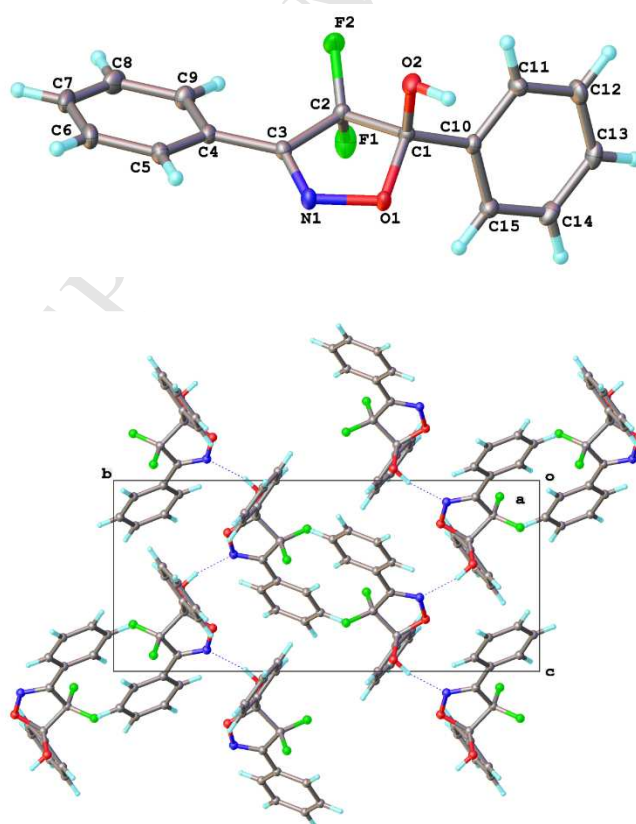


^a Isolated yield. ^b The reaction was carried out at 90 °C (reflux condition) in CH₃CN until full conversion of isoxazole. ^c The corresponding 4-fluoroisoxazole (**2e**) was isolated in 27%.

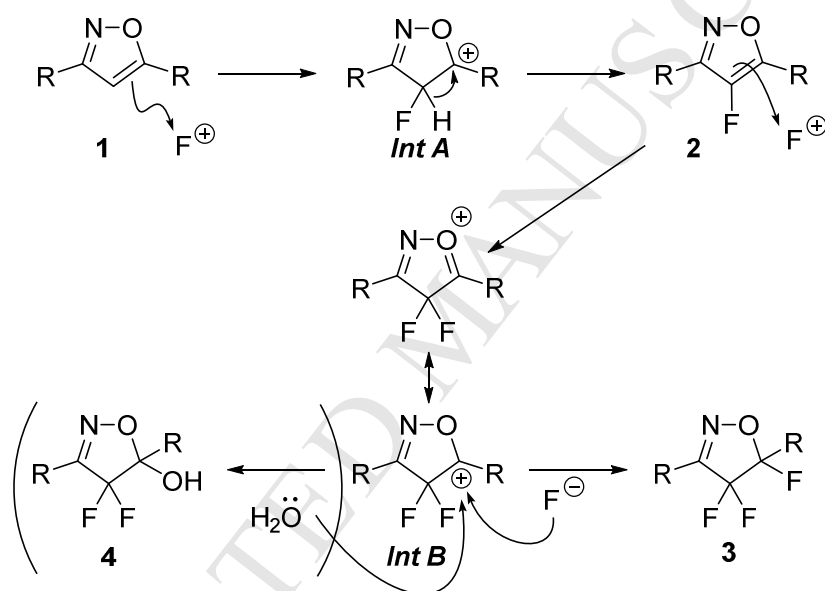
It was important to very rigorously dry the sulfolane solvent by vacuum distillation over sodium wire before attempting this trifluorination process because, when moist sulfolane was used (dry sulfolane from chemical suppliers used as received), a hydroxylated derivative was obtained after purification by column chromatography (Scheme 2).

Scheme 2. Synthesis of 4,4-difluoro-3,5-bis(phenyl)-isoxazol-5-ol derivatives (**4**).

The structures of **4a** and **4c** were confirmed by X-ray crystallography (Fig. 2). Both molecules adopt almost identical conformations in their crystals and are linked by O-H...N hydrogen bonds into infinite chains.

**Figure 2.** Molecular structure of 4,4-difluoro-3,5-diphenyl-isoxazol-5-ol (**4a**) and packing of the molecules in the crystal (hydrogen bonds are shown in dotted lines).

A mechanism for the formation of the monofluoro-, trifluoro and difluoro-hydroxyl systems is given in Scheme 2. Initial fluorination of the isoxazoles (**1**) gives the monofluorinated product (**2**) by a typical electrophilic aromatic substitution process. Since 4-fluoroisoxazoles are still significantly reactive towards electrophiles, reaction with a second equivalent of electrophilic fluorinating reagent SelectfluorTM gives difluorinated intermediates which are immediately trapped by fluoride ion to give 4,4,5-trifluoroisoxazolines (**3**) (Scheme 3). The source of fluoride ion in these reactions is most probably derived from the BF₄⁻ counterion of SelectfluorTM. The presence of any water in the sulfolane reaction medium gives rise to the hydroxyl group in (**4**).



Scheme 3. Proposed mechanism for selective fluorination of isoxazoles.

To provide a more consistent and readily operated synthesis of 4-fluoroisoxazole derivatives, we assessed a one-pot synthesis of 4-fluoroisoxazole **2** from the corresponding diketone **5** which in case of (**5c**), $R=R'=p\text{-Tol}$ exists in the disordered enol form in the crystal (Fig. 3).

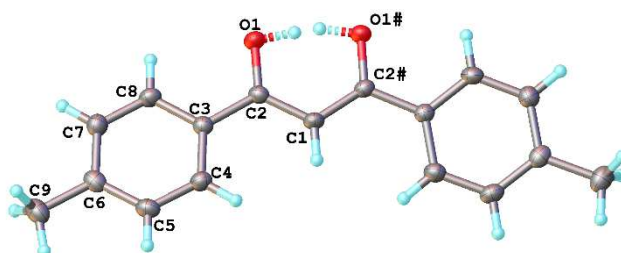
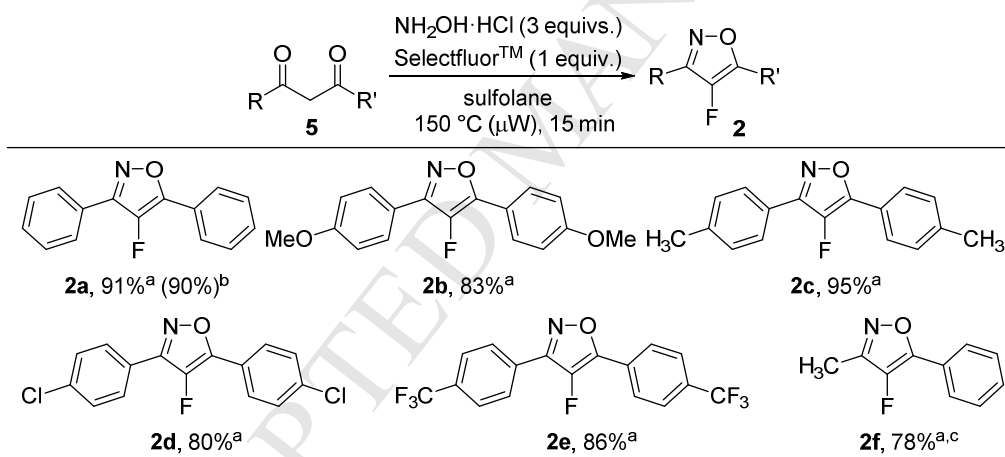


Figure 3. Molecular structure of diketone **5c** (R=R'=p-Tol, both components of disordered hydrogen atoms are shown).

Fortunately, reaction of diketone (**5**), hydroxylamine and SelectfluorTM in a single-pot, μ W assisted process provided a great improvement in the yield of fluoroisoxazole as shown in Table 4. By this one-pot process, 4-fluorinated isoxazoles were obtained together with a small amount of monofluorodiketone derivative in most cases but, even when 3 equivs. of SelectfluorTM was used, the corresponding 4,4,5-trifluoroisoxazolines (**3**) were not obtained. The presence of monofluorinated diketones in the reaction mixtures, as observed by ¹⁹F NMR spectroscopy, indicates that fluorination of the diketone substrates occurs before cyclisation leading to higher yields of the desired fluoroisoxazole products.

Table 4. One-pot synthesis of 4-fluoroisoxazole derivatives (**2**).



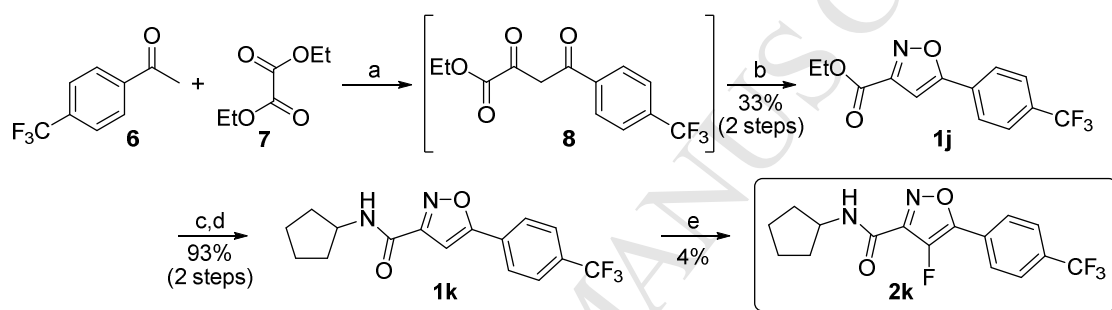
^a Isolated yield. ^b Isolated yield by using conventional heating (oil bath) at 150 °C for 1 h.

^c Regioisomeric mixtures (these isomers were calculated by ¹H NMR and its ratio was **2f** : its regioisomer = 86:14).

Based on the successful fluorination of isoxazoles, we used our methodology for the synthesis of a biologically active fluoroisoxazole system. Transient receptor potential vanilloid 1 (TRPV1) is a Ca^{2+} permeant non-selective cation channel expressed in a subpopulation of primary afferent neurons and led to the cloning of the first vanilloid (capsaicin) receptor by Julius and colleagues in 1997.⁸ Recently a new series of TRPV1 antagonists that are expected to aid in management of acute and chronic pain was reported and, 4-fluoroisoxazole-3-carboxyamides showed moderate potency in a TRPV1 assay.⁹ Using the synthetic methodology described above, we targeted the synthesis of 4-fluoroisoxazole-3-carboxamide (**2j**) following the strategy shown in Scheme 4

because this system has been reported to be a potent TRPV1 antagonist.^{9b} Reaction of diethyl oxalate and *p*-trifluoromethylacetophenone to form the corresponding diketoester (**8**) was followed by condensation with hydroxylamine hydrochloride to give the isoxazole (**1j**). Hydrolysis and amidation of **1j** gave the corresponding isoxazole-3-carboxamide (**1k**). The fluorination of **1k** as the final stage gave a desired TRPV1 antagonist (**2k**), although its yield was very low. To improve the yield, **1j** or related 3-hydroxymethyl-isoxazole (**1l**), were used as the substrates but no fluoroisoxazole products were obtained. Unfortunately, our one-pot strategy also failed to give higher yields of (**2k**) from (**8**) despite many attempts using a range of reaction conditions.

Scheme 4. Synthesis of 4-fluoroisoxazole-3-carboxamide as a TRPV1 antagonist.



^aLiHMDS, THF, -78 °C to rt, 1 h. ^bNH₂OH.HCl (2 equivs.), EtOH, reflux, 16 h. ^cLiOH, THF/H₂O, r.t., 1 h.

^doxalyl chloride, DMF, Et₃N, cyclopentylamine, CH₂Cl₂, 16 h. ^eSelectfluorTM (2 equivs.), sulfolane, 120 °C, 5 h.

3. Conclusions

In conclusion, we demonstrated that the C-4 fluorination of 3,5-disubstituted isoxazoles is possible when SelectfluorTM is used as the fluorinating agent using both conventional oil bath heating and μ W irradiation. We also showed that using an excess amount of SelectfluorTM gave the corresponding 4,4,5-trifluoroisoxazolines in moderate to good yields if thoroughly dry sulfolane is used as the reaction medium. The synthesis of 4-fluoroisoxazole derivatives can best be achieved in high yields by a one-pot process involving heating the 1,3-diketone substrate, SelectfluorTM and hydroxylamine in sulfolane using microwave heating.

4. Experimental

4.1 General Information

¹H NMR and ¹³C NMR spectra were recorded on JNM-GX400 spectrometers. ¹⁹F NMR spectra were recorded on Hitachi FT-NMR R-90H and Bruker 400 Ultrashield spectrometers. Chemical

shifts of ^1H NMR and ^{13}C NMR are reported in ppm from tetramethylsilane (TMS: 0 ppm) as an internal standard. Chemical shifts of ^{19}F NMR are reported in ppm from benzotrifluoride (BTF: 0 ppm) as an internal standard unless otherwise noted. All data are reported as follows: chemical shifts, relative integration value, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, br = broad, m = multiplet), coupling constants (Hz). Mass spectra were obtained on JEOL JMS-700T spectrometers and a Trace GC-MS device (Thermo-Finnigan Corporation) operating in electron impact ionization (EI) mode. Accurate mass analysis was performed on a Xevo QtoF mass spectrometer (Waters Ltd, UK) with an accurate solids analysis probe (ASAP). Melting points were measured on Yanagimoto micro melting point apparatus MP-S3. IR spectra were recorded on JASCO FT/IR-410 spectrophotometer. Analytical gas-liquid chromatography (GLC) was carried out on Hitachi G-3500 gas chromatograph (column; TO-5 0.25 mm x 15 m, carrier; He at 2.2 ml/min). Peak areas were calculated on Hitachi D-2500 Chromato-integrator. Microwave reactions were performed in microwave tubes with clip lids using Biotage Initiator microwave reactor. All commercially available reagents were used without further purification. All experiments were carried out under argon atmosphere unless otherwise noted.

4.2 General procedure for selective fluorination of isoxazoles to synthesise **2** assisted by μW irradiation.

Isoxazole (**1**; 1 mmol) and SelectfluorTM (1 mmol) were added to a microwave vial and suspended in sulfolane (4 mL). The vial was sealed and heated by microwave irradiation for 15 minutes at 150 °C. The resulting mixture was quenched with NaHCO_3 and, extracted with AcOEt. The AcOEt layer was washed with brine and dried over MgSO_4 . The solvent was removed *in vacuo* and the residue was purified by column chromatography to give 4-fluoroisoxazole (**2**).

4.3 General procedure for selective fluorination of isoxazoles to synthesise **2** heated by oil bath.

Under an Ar atmosphere, isoxazole (**1**; 1 mmol) and SelectfluorTM (1 mmol) were suspended in sulfolane (4 mL) and stirred for 1 h at 120 °C. The resulting mixture was quenched with NaHCO_3 and, extracted with AcOEt. The AcOEt layer was washed with brine and dried over MgSO_4 . The solvent was removed *in vacuo* and the residue was purified by column chromatography to give 4-fluoroisoxazole (**2**).

4.4 General procedure for the synthesis of 4,4,5-trifluoroisoxazoles **3**.

Under an Ar atmosphere, isoxazole (**1**; 1 mmol) and SelectfluorTM (3 mmol) were suspended in sulfolane (4 mL) and stirred for 1 h at 120 °C. The resulting mixture was quenched with NaHCO₃ and, extracted with AcOEt. The AcOEt layer was washed with brine and dried over MgSO₄. The solvent was removed *in vacuo* and the residue was purified by column chromatography to give 4-fluoroisoxazole (**3**).

4.5 General procedure for the synthesis of 4,4-difluoroisoxazol-5-ols **4**.

A mixture comprising of isoxazole (**1**, 1 mmol) and SelectfluorTM (3 mmol) in moist sulfolane (4 mL) was irradiated by microwave heating at 150 °C for 1 h. The product was extracted into chloroform, washed sequentially with sat. NaHCO₃ and brine, then dried (MgSO₄) and the solvent was removed *in vacuo*. Column chromatography on silica gel using hexane:ether:triethylamine (70:10:1) as eluent gave the 5-hydroxyl product (**4**).

4.6 General procedure for the one-pot synthesis of 4-fluorinated isoxazoles **2** assisted by μ W irradiation.

Diketone (**5**; 1 mmol), hydroxylamine hydrochloride (3 mmol) and SelectfluorTM (1 mmol) were added to a microwave vial and suspended in sulfolane (4 mL). The vial was sealed and heated by microwave irradiation for 15 minutes at 150 °C. The resulting mixture was quenched with NaHCO₃ and, extracted with AcOEt. The AcOEt layer was washed with brine and dried over MgSO₄. The solvent was removed *in vacuo* and the residue was purified by column chromatography to give 4-fluoroisoxazole (**2**).

4.7 Synthesis of ethyl 5-(4-(trifluoromethyl)phenyl)isoxazole-3-carboxylate (**1j**).

Under an Ar atmosphere, to a solution of *p*-trifluoromethylacetophenone (**6**; 2 mmol) and diethyl oxalate (**7**; 4 mmol) in THF (10 mL) was added 1.3 M of LiHMDS in THF (1.69 mL, 2.2 mmol) at -78 °C. The resulting mixture was gradually warmed to rt and stirred for 16 h. The mixture was quenched with 10% HCl and, extracted with AcOEt. The AcOEt layer was washed with brine and dried over MgSO₄. The solvent was removed *in vacuo* and, then the reaction residue was dissolved in EtOH (2 mL) and H₂O (3 mL). NH₂OH·HCl (278 mg, 4 mmol) was added and the resulting solution was heated at reflux for 16 h. The resulting mixture was quenched with brine and extracted with AcOEt, then dried over MgSO₄. The solvent was removed *in vacuo* and the residue was purified by column chromatography (SiO₂) to give the product (**1j**) (190 mg, 33 %).

4.8 Synthesis of *N*-cyclopentyl-5-(4-(trifluoromethyl)phenyl)isoxazole-3-carboxamide (**1k**).

To a solution of **1j** (285 mg, 1 mmol) in THF (5 mL) was added a solution of LiOH (71 mg, 1.7 mmol) in H₂O (5 mL) at rt and, the mixture was stirred for 1 h. The resulting mixture was quenched with 10% HCl, and extracted with AcOEt. The AcOEt layer was washed with brine and dried over MgSO₄. The solvent was removed *in vacuo* and, then the reaction residue was dissolved in CH₂Cl₂ (8 mL). A solution of oxalyl chloride (0.25 mL, 3 mmol) in CH₂Cl₂ (1.5 mL) was added to the residue solution and stirred for 20 min. A few drops of DMF were added and the mixture was stirred for 2 h at rt. The solvent was removed *in vacuo* and the residue was dissolved in CH₂Cl₂ (8 mL). Et₃N (0.5 mL) and cyclopentylamine (5 mL) were added and the solution was stirred for 16 h at rt. The resulting mixture was quenched with 10% HCl and extracted with AcOEt, then dried over MgSO₄. The solvent was removed *in vacuo* and the residue was purified by column chromatography (SiO₂) to give the product (**1k**) (300 mg, 93 %).

5. Spectroscopic Data

5.1 *Ethyl 5-(4-(trifluoromethyl)phenyl)isoxazole-3-carboxylate (1j)*. (0.09 g, 33%); colorless solid; M.p. 133.0–134.0 °C (recrystallized from EtOH); ¹H NMR (CDCl₃) δ: 1.46 (3H, t, *J* = 7.1 Hz), 4.50 (2H, q, *J* = 7.1 Hz), 7.04 (1H, s), 7.76–7.78 (2H, m), 7.93–7.96 (2H, m); ¹³C NMR (100 MHz, CDCl₃) δ: 14.46, 62.67, 101.6, 123.7 (q, *J* = 271.7 Hz), 126.4 (q, *J* = 3.8 Hz), 126.4, 129.8 (q, *J* = 1.3 Hz), 132.6 (q, *J* = 32.9 Hz), 157.3, 159.8, 170.1; ¹⁹F NMR (90 MHz, CDCl₃) δ: -0.31 (3F, s); MS *m/z*: 285 (M⁺); HRMS Calcd for C₁₃H₁₀F₃NO₃: 285.0613 (M⁺), Found: 285.0613; IR (KBr) cm⁻¹: 3134, 2990, 1725.

5.2 *N*-Cyclopentyl-5-(4-(trifluoromethyl)phenyl)isoxazole-3-carboxamide (**1k**). (0.30 g, 93%); colorless solid; M.p. 204.5–205.5 °C (recrystallized from EtOH); ¹H NMR (CDCl₃) δ: 1.51–1.81 (6H, m), 2.04–2.15 (2H, m), 4.41 (1H, m), 6.78 (1H, br d, *J* = 6.7 Hz), 7.07 (1H, s), 7.75–7.77 (2H, m), 7.91–7.93 (2H, m); ¹³C NMR (100 MHz, CDCl₃) δ: 23.74, 33.01, 51.33, 100.5, 123.5 (q, *J* = 271.7 Hz), 126.0 (q, *J* = 3.8 Hz), 126.1, 129.7 (q, *J* = 1.3 Hz), 132.2 (q, *J* = 32.9 Hz), 157.8, 159.3, 169.6; ¹⁹F NMR (90 MHz, CDCl₃) δ: -0.30 (3F, s); MS *m/z*: 324 (M⁺); HRMS Calcd for C₁₆H₁₅F₃N₂O₂: 324.1086 (M⁺), Found: 324.1084.

5.3 *4-Fluoro-3,5-diphenylisoxazole (2a)*. (0.10 g, 44%); colorless solid; M.p. 102.0–103.0 °C (recrystallized from EtOH); ^1H NMR (CDCl_3) δ : 7.45–7.55 (6H, m), 7.88–7.90 (2H, m), 7.94–7.97 (2H, m); ^{13}C NMR (100 MHz, CDCl_3) δ : 125.4 (d, $J = 4.9$ Hz), 126.1 (d, $J = 5.1$ Hz), 127.0 (d, $J = 3.9$ Hz), 127.2 (d, $J = 3.5$ Hz), 129.1 129.2, 130.3 (d, $J = 1.1$ Hz), 130.6, 141.7 (d, $J = 258.7$ Hz), 153.3 (d, $J = 10.6$ Hz), 153.7 (d, $J = 19.3$ Hz); ^{19}F NMR (90 MHz, CDCl_3) δ : -115.4 (1F, s); MS m/z : 239 (M^+); HRMS Calcd for $\text{C}_{15}\text{H}_{10}\text{NOF}$: 239.0746 (M^+), Found: 239.0755; IR (KBr) cm^{-1} : 3067, 1466, 1215.

5.4 *4-Fluoro-3,5-bis(4-methoxyphenyl)isoxazole (2b)*. (0.12 g, 41%); colorless solid; M.p. 137.0–138.0 °C (recrystallized from EtOH); ^1H NMR (CDCl_3) δ : 3.88 (3H, s), 3.88 (3H, s), 7.02–7.05 (4H, m), 7.80–7.90 (4H, m); ^{13}C NMR (100 MHz, CDCl_3) δ : 55.6, 55.7, 114.6, 114.7, 119.1 (d, $J = 5.1$ Hz), 119.7 (d, $J = 3.9$ Hz), 127.1 (d, $J = 4.8$ Hz), 128.7 (d, $J = 3.7$ Hz), 140.7 (d, $J = 255.4$ Hz), 152.9 (d, $J = 10.5$ Hz), 153.5 (d, $J = 19.7$ Hz), 161.0 (d, $J = 1.5$ Hz), 161.4; ^{19}F NMR (90 MHz, CDCl_3) δ : -117.5 (1F, s); MS m/z : 299 (M^+); HRMS Calcd for $\text{C}_{17}\text{H}_{14}\text{NO}_3\text{F}$: 299.0958 (M^+), Found: 299.0959; IR (KBr) cm^{-1} : 2973, 2944, 1648, 1609, 1516, 1467, 1252.

5.5 *4-Fluoro-3,5-di-p-tolylisoxazole (2c)*. (0.11 g, 44%); colorless solid; M.p. 152.5–153.0 °C (recrystallized from EtOH); ^1H NMR (CDCl_3) δ : 2.43 (6H, s), 7.31–7.34 (4H, m), 7.76–7.84 (4H, m); ^{13}C NMR (100 MHz, CDCl_3) δ : 21.50, 21.54, 123.1 (d, $J = 5.0$ Hz), 123.9 (d, $J = 3.9$ Hz), 125.0 (d, $J = 4.9$ Hz), 126.7 126.8, 129.5 (d, $J = 5.3$ Hz), 140.2 (d, $J = 1.3$ Hz), 140.5, 141.0 (d, $J = 256.8$ Hz), 152.9 (d, $J = 10.5$ Hz), 153.4 (d, $J = 19.4$ Hz); ^{19}F NMR (90 MHz, CDCl_3) δ : -116.1 (1F, s); MS m/z : 267 (M^+); HRMS Calcd for $\text{C}_{17}\text{H}_{14}\text{NOF}$: 267.1059 (M^+), Found: 267.1068; IR (KBr) cm^{-1} : 1647, 1614, 1514, 1470.

5.6 *3,5-Bis(4-chlorophenyl)-4-fluoroisoxazole (2d)*. (0.11 g, 35%); colorless solid; M.p. 170.0–172.0 °C (recrystallized from EtOH); ^1H NMR (CDCl_3) δ : 7.48–7.53 (4H, m), 7.80–7.83 (2H, m), 7.87–7.89 (2H, m); ^{13}C NMR (100 MHz, CDCl_3) δ : 124.3 (d, $J = 5.1$ Hz), 125.2 (d, $J = 4.0$ Hz), 126.7 (d, $J = 5.0$ Hz), 128.5 (d, $J = 3.7$ Hz), 129.6, 129.7, 136.6 (d, $J = 1.9$ Hz), 137.0 (d, $J = 0.7$ Hz), 141.6 (d, $J = 258.7$ Hz), 152.5 (d, $J = 10.5$ Hz), 153.0 (d, $J = 19.4$ Hz); ^{19}F NMR (90 MHz, CDCl_3) δ : -114.6 (1F, s); MS m/z : 307 (M^+); HRMS Calcd for $\text{C}_{15}\text{H}_8\text{NOCl}_2\text{F}$: 306.9967 (M^+), Found: 306.9969; IR (KBr) cm^{-1} : 1651, 1599, 1496, 1457, 1092.

5.7 *4-Fluoro-3,5-bis(4-(trifluoromethyl)phenyl)isoxazole (2e)*. (0.06 g, 16%); colorless solid; M.p. 156.0–157.0 °C (recrystallized from EtOH); ^1H NMR (CDCl_3) δ : 7.79–7.82 (4H, m), 8.00–8.09 (4H, m); ^{13}C NMR (100 MHz, CDCl_3) δ : 123.5 (q, $J = 271.7$ Hz), 123.5 (q, $J = 271.6$ Hz), 125.4 (d, $J = 5.2$ Hz), 125.9 (q, $J = 3.8$ Hz), 126.1 (q, $J = 3.8$ Hz), 127.3 (d, $J = 3.7$ Hz), 128.5 (m), 129.6 (m), 131.9 (qd, $J = 32.8, 1.5$ Hz), 132.4 (q, $J = 32.8$ Hz), 142.1 (d, $J = 261.1$ Hz), 152.1 (d, $J = 10.4$ Hz), 152.5 (d, $J = 19.5$ Hz); ^{19}F NMR (90 MHz, CDCl_3) δ : -0.29 (6F, s), -113.1 (1F, s); MS m/z : 375 (M^+); HRMS Calcd for $\text{C}_{17}\text{H}_8\text{NOF}_7$: 375.0494 (M^+), Found: 375.0498; IR (KBr) cm^{-1} : 1650, 1619, 1538, 1321, 1175, 1136.

5.8 *4-Fluoro-3-methyl-5-phenylisoxazole (2f)*. (0.07 g, 71%); colorless oil; ^1H NMR (CDCl_3) δ : 2.37 (3H, d, $J = 0.5$ Hz), 7.40–7.51 (3H, m), 7.79–7.82 (2H, m); ^{13}C NMR (100 MHz, CDCl_3) δ : 8.70 (d, $J = 5.8$ Hz), 125.0 (d, $J = 4.8$ Hz), 125.8 (d, $J = 5.0$ Hz), 128.8, 129.7 (d, $J = 1.3$ Hz), 142.1 (d, $J = 254.9$ Hz), 151.7 (d, $J = 15.9$ Hz), 151.8 (d, $J = 18.2$ Hz); ^{19}F NMR (90 MHz, CDCl_3) δ : -118.3 (1F, s); MS m/z : 177 (M^+); HRMS Calcd for $\text{C}_{10}\text{H}_8\text{FNO}$: 177.0590 (M^+), Found: 177.0586.

5.9 *N-Cyclopentyl-4-fluoro-5-(4-(trifluoromethyl)phenyl)isoxazole-3-carboxamide (2k)*. (0.01 g, 4%); colorless solid; M.p. 188.5–189.0 °C (recrystallized from MeOH); ^1H NMR (CDCl_3) δ : 1.52–1.78 (6H, m), 2.07–2.15 (2H, m), 4.42 (1H, m), 6.62 (1H, br d, $J = 6.1$ Hz), 7.78–7.80 (2H, m), 7.96–7.98 (2H, m); ^{13}C NMR (100 MHz, CDCl_3) δ : 23.7, 33.0, 51.3, 123.4 (q, $J = 271.8$ Hz), 125.4 (d, $J = 4.8$ Hz), 126.1 (q, $J = 3.8$ Hz), 128.1 (m), 132.1 (m), 142.1 (d, $J = 266.6$ Hz), 148.7 (d, $J = 8.5$ Hz), 153.5 (d, $J = 17.9$ Hz), 156.2 (d, $J = 3.7$ Hz); ^{19}F NMR (90 MHz, CDCl_3) δ : -0.37 (3F, s), -111.0 (1F, s); MS m/z : 342 (M^+); HRMS Calcd for $\text{C}_{16}\text{H}_{14}\text{F}_4\text{N}_2\text{O}_2$: 342.0991 (M^+), Found: 342.0995.

5.10 *4,4,5-Trifluoro-3,5-diphenyl-4,5-dihydroisoxazole (3a)*. (0.22 g, 78%); colorless oil; ^1H NMR (CDCl_3) δ : 7.48–7.58 (6H, m), 7.66–7.68 (2H, m), 7.88–7.90 (2H, m); ^{13}C NMR (100 MHz, CDCl_3) δ : 111.3 (ddd, $J = 241.5, 36.5, 21.1$ Hz), 124.1 (m), 124.8 (ddd, $J = 290.5, 256.1, 34.4$ Hz), 127.3 (m), 127.4 (d, $J = 1.7$ Hz), 128.3 (m), 128.9, 129.5, 131.4 (d, $J = 1.7$ Hz), 132.5, 154.8 (dd, $J = 25.6, 23.7$ Hz); ^{19}F NMR (90 MHz, CDCl_3) δ : -38.4 (1F, dd, $J = 273, 8$ Hz), -52.9 (1F, dd, $J = 8, 3$ Hz), -61.0 (1F, dd, $J = 273, 3$ Hz); MS m/z : 277 (M^+); HRMS Calcd for $\text{C}_{15}\text{H}_{10}\text{NOF}_3$: 277.0714 (M^+), Found: 277.0716; IR (neat) cm^{-1} : 3067, 1140, 1057, 1039.

5.11 *4,4,5-Trifluoro-3,5-bis(4-methoxyphenyl)-4,5-dihydroisoxazole (3b)*. (0.20 g, 59%); colorless solid; M.p. 59.5–61.5 °C (recrystallized from hexane); ¹H NMR (CDCl₃) δ: 3.86 (s, 3H), 3.87 (s, 3H), 6.99–7.02 (4H, m), 7.56–7.59 (2H, m), 7.82–7.84 (2H, m); ¹³C NMR (100 MHz, CDCl₃) δ: 55.31, 55.39, 111.0 (ddd, *J* = 239.7, 36.1, 21.2 Hz), 113.9, 114.6, 116.1 (dd, *J* = 3.0, 1.4 Hz), 119.9 (dd, *J* = 27.9, 0.9 Hz), 124.4 (ddd, *J* = 271.9, 254.6, 35.4 Hz), 128.4 (dd, *J* = 5.2, 1.4 Hz), 128.7 (d, *J* = 1.9 Hz), 154.0 (dd, *J* = 25.3, 23.7 Hz), 161.5 (d, *J* = 1.8 Hz), 162.5; ¹⁹F NMR (90 MHz, CDCl₃) δ: -38.3 (1F, dd, *J* = 273, 8 Hz), -51.6 (1F, dd, *J* = 8, 4 Hz), -61.0 (1F, dd, *J* = 273, 4 Hz); MS *m/z*: 337 (M⁺); HRMS Calcd for C₁₇H₁₄F₃NO₃: 337.0926 (M⁺), Found: 337.0923; IR (KBr) cm⁻¹: 2967, 2936, 1613, 1518, 1265.

5.12 *4,4,5-Trifluoro-3,5-di-p-tolyl-4,5-dihydroisoxazole (3c)*. (0.17 g, 56%); colorless solid; M.p. 73.0–74.0 °C (recrystallized from MeOH); ¹H NMR (CDCl₃) δ: 2.42 (m, 6H), 7.29–7.31 (4H, m), 7.53–7.55 (2H, m), 7.76–7.78 (2H, m); ¹³C NMR (100 MHz, CDCl₃) δ: 21.39, 21.65, 110.6 (ddd, *J* = 240.2, 36.2, 21.1 Hz), 120.9 (m), 124.5 (ddd, *J* = 272.1, 255.0, 34.7 Hz), 125.0 (m), 126.8 (m), 126.9 (d, *J* = 1.8 Hz), 129.1, 129.8, 141.2 (d, *J* = 1.8 Hz), 142.7, 154.4 (dd, *J* = 25.5, 23.6 Hz); ¹⁹F NMR (90 MHz, CDCl₃) δ: -38.4 (1F, dd, *J* = 273, 8 Hz), -52.4 (1F, dd, *J* = 8, 4 Hz), -61.1 (1F, dd, *J* = 273, 4 Hz); MS *m/z*: 305 (M⁺); HRMS Calcd for C₁₇H₁₄F₃NO: 305.1027 (M⁺), Found: 305.1035; IR (KBr) cm⁻¹: 2969, 1136, 1042.

5.13 *3,5-Bis(4-chlorophenyl)-4,4,5-trifluoro-4,5-dihydroisoxazole (3d)*. (0.23 g, 66%); colorless solid; M.p. 111.0–111.5 °C (recrystallized from hexane); ¹H NMR (CDCl₃) δ: 7.48–7.51 (4H, m), 7.57–7.59 (2H, m), 7.80–7.82 (2H, m); ¹³C NMR (100 MHz, CDCl₃) δ: 110.6 (ddd, *J* = 241.9, 36.2, 21.2 Hz), 121.9 (m), 124.2 (ddd, *J* = 272.6, 255.6, 34.1 Hz), 126.2 (m), 128.2 (d, *J* = 1.8 Hz), 128.3 (m), 128.9, 129.6, 137.6 (d, *J* = 2.2 Hz), 138.7, 153.7 (dd, *J* = 25.6, 23.8 Hz); ¹⁹F NMR (90 MHz, CDCl₃) δ: -38.5 (1F, dd, *J* = 274, 8 Hz), -53.0 (1F, dd, *J* = 8, 4 Hz), -60.9 (1F, dd, *J* = 274, 4 Hz); MS *m/z*: 345 (M⁺); HRMS Calcd for C₁₅H₈Cl₂F₃NO: 344.9935 (M⁺), Found: 344.9928; IR (KBr) cm⁻¹: 3097, 1094, 1046.

5.14 *4,4,5-Trifluoro-3-methyl-5-phenyl-4,5-dihydroisoxazole (3f)*. (0.14 g, 67%); colorless oil; ¹H NMR (CDCl₃) δ: 2.23 (3H, d, *J* = 2.3 Hz), 7.45–7.55 (3H, m), 7.58–7.60 (2H, m); ¹³C NMR (100 MHz, CDCl₃) δ: 8.59 (m), 109.9 (ddd, *J* = 239.4, 36.3, 20.4 Hz), 123.9 (ddd, *J* = 270.2, 254.1, 34.6 Hz), 126.8 (dd, *J* = 5.2, 1.6 Hz), 128.1 (dd, *J* = 27.0, 1.1 Hz), 128.4, 130.9 (d, *J* = 1.9 Hz), 154.4 (dd, *J* = 28.5, 24.6 Hz); ¹⁹F NMR (90 MHz, CDCl₃) δ: -43.9 (1F, m), -53.8 (1F, m), -66.3 (1F, m); MS

m/z : 215 (M^+); HRMS Calcd for $C_{10}H_8F_3NO$: 215.0558 (M^+), Found: 215.0559; IR (KBr) cm^{-1} : 3069, 1147, 1114, 1043.

5.15 *4,4-Difluoro-3,5-diphenyl-isoxazol-5-ol (4a)*. (0.08 g, 30%); orange powder; M.p. 103–106 °C; 1H NMR ($CDCl_3$) δ : 3.73 (1H, s), 7.58–7.46 (6H, m), 7.71–7.67 (2H, m), 7.89 (2H, d, $J = 7.2$ Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ : 126.83 (d, $J = 1.4$ Hz), 127.04 (d, $J = 1.5$ Hz), 128.59, 129.08, 130.36, 131.60; ^{19}F (376 MHz, internal standard: $CFCl_3$ as 0 ppm, $CDCl_3$) δ : -100.39 (d, $J = 266.3$ Hz), -120.09 (d, $J = 266.3$ Hz); HRMS Calcd for $C_{15}H_{12}F_2NO$: 276.0841 ($[MH]^+$), Found: 276.0842; IR (neat) cm^{-1} : 2982, 1450, 1365, 1242, 1127, 1098.

5.16 *4,4-Difluoro-3,5-bis(4'-methylphenyl)-isoxazol-5-ol (4c)*. (0.06 g, 19%); orange powder; M.p. 119–122 °C; 1H NMR (400 MHz, $CDCl_3$) δ : 2.40 (3H, s), 2.41 (3H, s), 3.92 (1H, s), 7.30–7.24 (4H, m), 7.54 (2H, d, $J = 8.2$ Hz), 7.75 (2H, d, $J = 8.1$ Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ : 21.33, 21.62, 126.75 (d, $J = 1.4$ Hz), 126.95 (d, $J = 1.3$ Hz), 128.27, 129.79, 140.42, 142.10; ^{19}F (376 MHz, internal standard: $CFCl_3$ as 0 ppm, $CDCl_3$) δ : -100.26 (d, $J = 265.6$ Hz), -120.53 (d, $J = 265.8$ Hz); HRMS Calcd for $C_{17}H_{16}NF_2O$: 304.1140 ($[MH]^+$), Found: 304.1137; IR (neat) cm^{-1} : 1362, 1243, 1128, 1091, 1027.

6. X-Ray crystallography

The single crystal X-ray diffraction data for the compound **5** have been collected on an Agilent XCalibur diffractometer (Sapphire-3 CCD detector, graphite monochromator,) and for all other compounds on a Bruker D8 Venture (Photon 100 CMOS detector, I μ S microsource, focusing mirrors) diffractometer using $\lambda MoK\alpha$ radiation, $\lambda = 0.71073 \text{ \AA}$. All data were collected at the temperature 120.0(2)K maintained by Cryostream (Oxford Cryosystems) open-flow nitrogen cryostats. The structures were solved by direct method and refined by full-matrix least squares on F^2 for all data using SHELXTL¹⁰ and Olex2¹¹ software. All non-disordered non-hydrogen atoms were refined anisotropically, hydrogen atoms were placed in the calculated positions and refined in riding mode. The disordered atoms were refined with fixed $SOF=0.5$ in isotropic approximation. The structure **2c** shows the whole molecule disorder and was refined isotropically with a number of geometry constraints. The crystallographic data and refinement parameters are shown in Table 5,

crystallographic data for the structure have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication CCDC-1440941-1440946.

Table 5. Crystal data and structure refinement

Compound	2a	2c	2d	4a	4c	5c
Empirical formula	C ₁₅ H ₁₀ FNO	C ₁₇ H ₁₄ FNO	C ₁₅ H ₈ Cl ₂ FNO	C ₁₅ H ₁₁ F ₂ NO ₂	C ₁₇ H ₁₅ F ₂ NO ₂	C ₁₇ H ₁₆ O ₂
Formula weight	239.24	267.29	308.12	275.25	303.30	252.30
Crystal system	tetragonal	triclinic	monoclinic	monoclinic	monoclinic	monoclinic
Space group	P4 ₁	P1	P2 ₁ /c	P2 ₁ /c	P2 ₁ /n	C2/c
a/Å	17.2287(16)	4.9701(8)	14.3733(2)	8.37740(10)	12.7558(3)	11.2849(8)
b/Å	17.2287(16)	6.9708(10)	7.58840(10)	18.4265(3)	8.4290(2)	11.8771(5)
c/Å	23.098(2)	9.8488(13)	12.2635(3)	8.60770(10)	14.8259(4)	10.6797(7)
α/°	90.00	86.142(11)	90.00	90.00	90.00	90.00
β/°	90.00	85.356(12)	105.1303(13)	106.7387(15)	106.521(2)	114.044(8)
γ/°	90.00	81.025(12)	90.00	90.00	90.00	90.00
Volume/Å ³	6856.0(11)	335.42(8)	1291.22(4)	1272.44(3)	1528.25(7)	1307.23(14)
Z	24	1	4	4	4	4
ρ _{calc} /cm ³	1.391	1.323	1.585	1.437	1.318	1.282
μ/mm ⁻¹	0.099	0.092	0.507	0.115	0.103	0.083
Reflections collected	86503	6768	27038	19475	19890	7898
Independent refl., R _{int}	7647, 0.1995	1787, 0.0729	3765, 0.0481	3387, 0.0372	3330, 0.0585	1745, 0.0507
Data/restraints/parameters	7647/1/974	1787/3/117	3765/0/213	3387/0/185	3330/0/205	1745/1/94
Goodness-of-fit on F ²	1.013	1.415	1.051	1.008	1.033	1.025
Final R ₁ [I ≥ 2σ (I)]	0.0686	0.1247	0.0340	0.0422	0.0708	0.0603
Final wR ₂ [all data]	0.1816	0.4073	0.0926	0.1136	0.2084	0.1784

7. Acknowledgments

We thank Durham University M. Chem. Undergraduate program for funding.

8. References and notes

- (a) Fluorine-Containing Synthons; Soloshonok, V. A. Ed.; ACS Publications Division and Oxford University Press: Washington, D.C., 2005. (b) Uneyama, K. Organofluorine Chemistry; Blackwell Publishing: Oxford, 2006. (c) Bégué, J.-P., Bonnet-Delpon, D.; Bioorganic and Medicinal Chemistry of Fluorine; John Wiley & Sons Ltd.: New Jersey, 2008. (d) Fluorine in Medicinal Chemistry and Chemical Biology; Ojima, I., Ed.; Wiley-Blackwell: Chichester, 2009.
- For the synthesis of fluorinated pyridine: (a) Umemoto, T.; Tomizawa, G. J. Org. Chem. 1989, 54, 1726–1731. (b) Stavber, S.; Zupan, M. Tetrahedron Lett. 1990, 31, 775–776. (c) Gakh, A. A.; Tuinman, A. A.; Adcock, J. L.; Compton, R. N. Tetrahedron Lett. 1993, 34, 7167–7170. (d) O'Neill, P. M.; Storr, R. C.; Kevin Park, B. Tetrahedron 1998, 54, 4615–4622. (e) Fang, B.; Tao, H.; Kan, X.; Shang, Y. Heterocyclic Commun. 2004, 10, 305–306.

3. For the synthesis of fluorinated pyrimidine: (a) Robins, M. J.; Naik, S. R. *J. Chem. Soc., Chem. Commun.*, 1972, 18–19. (b) Yemul, S. S.; Kagan, H. B. *Tetrahedron Lett.* 1980, 21, 277–280. (c) Boudakian, M. M.; Hyde, G. A. *J. Fluorine Chem.* 1984, 25, 435–446. (d) Cabaj, J. E.; Wuts, P. G. M.; Henegar, K. E. *J. Org. Chem.* 1994, 59, 5090–5092. (e) Rangwala, H. S.; Giraldez, J. W.; Gurvich, V. J., *J. Labelled Compd. Radiopharm.* 2011, 54, 340–343.
4. For the synthesis of fluorinated pyrazole: (a) Sloop, J. C.; Jackson, J. L.; Schmidt, R. D. *Heteroat. Chem.* 2009, 20, 341–345. (b) Qian, J.; Liu, Y.; Zhu, J. Jiang, B.; Xu, Z. *Org. Lett.* 2011, 13, 4220–4223.
5. For the synthesis of fluorinated isoxazole: (a) Bumgardner, C.L.; Sloop, J.C. *J. Fluorine Chem.* 1992, 56, 141–146. (b) Jeong, Y.; Kim, B.-I.; Lee, J. K.; Ryu, J.-S. *J. Org. Chem.* 2014, 79, 6444–6455. (c) Stephens, C. E.; Blake, J. A. *J. Fluorine Chem.* 2004, 125, 1939–1945.
6. For the synthesis of fluorinated thiazole: (a) Campbell, T. F.; Stephens, C. E. *J. Fluorine Chem.* 2006, 127, 1591–1594. (b) Hatfield, J. M.; Eidell, C. K.; Stephens, C. E. *Tetrahedron Lett.* 2013, 54, 1025–1028.
7. (a) Breen, J. R.; Sandford, G.; Yufit, D. S.; Howard, J. A. K.; Fray, J.; Patel, B. *Beilstein J. Org. Chem.* 2011, 7, 1048–1054. (b) Breen, J. R.; Sandford, G.; Patel, B.; Fray, J. *Synlett* 2015, 26, 51–54.
8. (a) Caterina, M. J.; Schumacher, M. A.; Tominaga, M.; Rosen, T. A.; Levine, J. D.; Julius, D. *Nature* 1997, 389, 816–824. (b) Szallasi, A.; Cortright, D. N.; Blum, C. A.; Eid, S. R. *Nat. Rev. Drug Discovery* 2007, 6, 357–372.
9. (a) Palin, R.; Abernethy, L.; Ansari, N.; Cameron, K.; Clarkson, T.; Dempster, M.; Dunn, D.; Easson, A.-M.; Edwards, D.; Maclean, J.; Everett, K.; Feilden, H.; Ho, K.-K.; Kultgen, S.; Littlewood, P.; McArthur, D.; McGregor, D.; McLuskey, H.; Neagu, I.; Neale, S.; Nisbet, L.-A.; Ohlmeyer, M.; Pham, Q.; Ratcliffe, P.; Rong, Y.; Roughton, A.; Sammons, M.; Swanson, R.; Tracey, H.; Walker, G. *Bioorg. Med. Chem. Lett.* 2011, 21, 892–898. (b) Roughton, A. L.; Ho, K.-K.; Ohlmeyer, M.; Neagu, I.; Kultgen, S. G.; Ansari, N.; Rong, Y.; Ratcliffe, P. D.; Palin, R. *PCT Int. Appl. WO2009016241 A1*, 2009.
10. Sheldrick, G. M., *Acta Cryst., Sect. A*: 2008, 64, 112–122.
11. Dolomanov, O. V., Bourhis, L. J., Gildea, R. J., Howard, J. A. K., Puschmann H., *J. Appl. Cryst.*, 2009, 42, 339–341.